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See article on Hansen's Disease. p. 268

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AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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EDITORIAL

THE PRESCRIPTION STUDY AND ITS IMPLICATIONS

THE prescription study conducted by the Pharmaceutical Survey led to a number of statistical data from which may be drawn certain conclusions of importance to pharmacy.

First, we wish to compliment those who conducted this study and, in particular, J. Solon Mordell, the then Assistant Director of the Pharmaceutical Survey, under whose direction the prescription study was carried out. The meticulous care and precision of his work is more than evident in a perusal of the published study * and we strongly endorse its reading by all those interested in trends of prescription practice in the United States.

The prescriptions for the study were obtained from all sections of the country. They were selected from both towns and cities varying widely in population. The pharmacies were of all types: average drug stores, professional stores and chain operated stores. Each store was asked to submit copies of all prescriptions filled on a representative day during the first fifteen days of November 1946. A total of 13,125 prescriptions were tabulated. These came from 220 pharmacies located in 186 communities, representing 39 states.

As might be expected, anti-infectives and vitamins topped the list relative to the type of therapy prescribed. The former comprised 15.3 per cent and the latter 10.4 per cent of the total. Sedatives and hypnotics were a close third with 9.2 per cent followed by autonomic drugs, 8.5 per cent; analgesics, 8.4 per cent; gastrointestinal drugs, 7.6 per cent and others with lower frequency.

Dental prescriptions accounted for only 0.8 per cent of the total. This fact gives ample support to the oft-repeated statement that the dental profession is an untapped reservoir of prescription business for the pharmacist.

* Available from American Council on Education, Washington, D. C.

New prescriptions represented 65.2 per cent of the total and refills 34.8 per cent. Of the refills 74.1 per cent were refilled less than a year from their date of issue; 11.8 per cent, one to two years; 9.2 per cent, two to four years; 2.5 per cent, four to six years and 2.4 per cent over six years.

Since 34.8 per cent of total prescription volume was in refills it is easy to see the reason for the great opposition that has arisen to any reform or curtailment of this activity by pharmacists. From the standpoint of purely objective reasoning one cannot justify the present system of unlimited refills now currently in use. We have spoken of this evil before and we do so now again. Those who insist that a prescription should be subject to refill as desired by the patient are not only short-sighted but also, in all likelihood, motivated only by self-interest.

Compounded prescriptions, i. e., those requiring the mixing of two or more ingredients or one manufactured by the pharmacist, accounted for only 25.9 per cent of the total as compared with dispensed prescriptions which made up the balance of 74.1 per cent. Prescription specialties were prescribed or used in 60.8 per cent of the total. This is a continuing trend which is based on the discovery of specifics for the treatment of various diseases and the rapid growth of prescription specialties which are heavily detailed to physicians. This development has both advantages and disadvantages. No one can deny that the health of the general public is vastly improved over that of the "good old days" when pharmacists prided themselves on their ability to mix ten or more ingredients, even though it made therapeutic nonsense. We must recognize the fact that pharmacy today is highly specialized. No one individual can expect to do all of the tasks of pharmacy any more than one man could build a modern automobile. The medical profession, too, is highly specialized. It has its pathologists, allergists, gynecologists, cardiologists, etc. Pharmacists, today, must specialize in manufacturing, control, distribution, detailing, prescription filling, etc. To understand thoroughly every aspect of pharmacy is practically impossible just as it would be entirely impractical to manufacture in the drug store all products dispensed on prescription.

The prescription pharmacist need not feel that his services are unimportant, they have changed and for the better. Not only is he an essential link in the system of distribution but more and more he has become a true ally of the physician in guiding him in his selection and use of drugs. The pharmacist with vision, today, looks to this new role with satisfaction and prepares himself to meet the challenge that the future offers.

One serious problem created by the growth of prescription specialties is duplication. Many retail pharmacists are concerned over the tremendous inventory that must be carried in the prescription department and the high rate of obsolescence. This problem will not be discussed fully now but it is one that the pharmaceutical industry should give some attention, and soon, unless it is prepared to see fewer retail outlets and increased cost of medical care. The latter is particularly precarious if socialized medicine is to be avoided.

To return to the prescription study, the average price charged for a prescription was $1.45, the median price, $1.00, and the modal price, $1.00. From these figures it is apparent that prescription prices have not increased to an excessive degree. It is likely that they still are not in proportion to the cost of living index as compared with the 1939-41 level. This speaks well for the structure of pharmacy and its effort to serve the public interest. Few other fields outside the health professions can show a similar restraint.

The prescription ingredient analysis was a major part of the study. A frequency analysis was made on each of the 2400 drugs that appeared. Recognition was given to the fact that a drug might be prescribed as such or as an ingredient of some preparation. It is interesting to note that thiamin hydrochloride ranked number 1 in frequency of use and five other vitamins were among the first ten.

Space does not permit further discussion of the prescription study's findings. We feel that this study was a very useful and constructive part of the overall task of the Pharmceutical Survey. It is quite possible that, with the technic developed, future studies may be made from time to time. Such effort would be well worth the cost in helping the industry and the profession plan for the future.

L. F. Tice

THE POTENTIATING EFFECTS OF VARIOUS COMPOUNDS ON THE ANTI-BACTERIAL ACTIVITIES OF SURFACE ACTIVE AGENTS

By Louis Gershenfeld, D. Sc., and Russell L. Stedman, D. Sc.*

Part I

THE systemic investigation of the potentiating effects of combinations of different antibacterial agents constantly presents new possibilities. Data on the physiological and biochemical activities of bacteria are being rapidly accumulated and are helpful in planning studies on the efficiencies of combinations of antibacterial agents. The admixture of two toxic agents, each of which is an antagonist or inhibitor of a specific metabolic process frequently results in an increase of their antibacterial efficiencies. This has been shown with mixtures of penicillin and sulfadiazine tested *in vitro* (1). The use of a trace metal (2) in combination with penicillin has resulted in potentiation when tested *in vivo* (3). The action of combinations of surface active agents with sulfonamides, mercurials and hexylresorcinol has been reported by Gershenfeld and his co-workers (4, 5). The enhancing properties of pterins and sulfathiazole (6), penicillin or sulfonamides and urea (7), Aerosol and mercurials or hexylresorcinol (8), urea and phenol or cresol derivatives (9), surface active agents with subtilin (10), and combinations of antibiotics (11) have been demonstrated. Gershenfeld and Sagin (4) and Kolmer (12) presented bibliographies of other laboratory and clinical studies in which combinations of antibacterial agents were employed.

The application of metabolic data to the use of mixtures of antibacterial agents directed against Gram negative species has proven interesting. Dubos (13) stated that the presence of a phospholipid-protein-polysaccharide complex may contribute to the greater resistance of these organisms. Cephalin, the phospholipid component of this complex, is an inhibitor of a large number of antibacterial agents. Miller *et al.* (14) have noted that combinations of pro-

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tamine sulfate (a cephalin inhibitor) and tyrothricin result in a potentiation against *E. coli*. The antibiotic alone is ineffective against this organism. These workers indicate that acridines may act in the same way as protamines.

9-amino acridine, the most basic and most active of the commonly found acridine derivatives (13), was used by the British and Australian Armies during the last war (15). Extensive studies on the *in vitro* (16, 17) and *in vivo* (18) antibacterial activity of 9-amino acridine have been made. This acridine compound probably possesses the ability to inactivate cephalin. This property led to the choice of 9-amino acridine as a potentiating agent for surface active agents in this study. Neutralization of the cephalin in the protective complex of Gram negative organisms should permit higher dilutions of surface active agents to be effective.

Pratt and co-workers (3, 19, 20) have studied the antibacterial activities of mixtures of penicillin and cobalt chloride against *E. coli* and *S. aureus*. These workers assign the mode of action of the trace metal to the formation of complexes with sulfhydryl groups in components of essential oxidation-reduction systems. The inhibition of the oxidation of cysteine by cobalt sulfate at very low concentrations has been demonstrated (21). Such an inhibition might supplement the mode of action of quaternary ammonium compounds as reviewed by Rahn and Van Eseltine (22).

In addition to 9-amino acridine and cobalt chloride, it was decided to study the effect of a non-ionic surface active agent on cationic and anionic surface active agents. Baker *et al.* (23) have shown that Demal, a non-ionic mixture of polyglycerol esters, was effective in preventing the inhibition of Zephiran and Tergitol 7 against *S. aureus*. Manometric measurement of aerobic glycolysis was used as a criterion for antiseptic antagonism. Hotchkiss (24) briefly mentioned non-ionic detergents and phospholipids as being potent neutralizers of the antibacterial action of cationic surface active agents. An industrial technical bulletin (25) indicated that mixtures containing a high proportion of non-ionic agent to cationic agent seriously affects the germicidal action of the latter. On the other hand, another technical bulletin (26) stated that no reduction in the germicidal activity of Hyamine 1622 (cationic) occurs in mixtures of this agent with a series of non-ionic agents; included

in the series were Triton X-100, Triton X-155 and Triton A-20. A mixture containing 5% Hyamine 1622 and 5% Triton X-100 in an alkaline solution of tetrasodium pyrophosphate was recommended.

Purpose

This investigation was undertaken to determine the effect of cobalt chloride ($CoCl_2.6H_2O$), 9-amino acridine and a non-ionic surface active agent (Triton N-100) on the *in vitro* bacteriostatic efficiencies of five cationic surface active agents (Emulsept, BTC, Isothan Q-15, Ceepryn and CTAB) and one anionic surface active agent (Duponol C).

Procedure

A modification of the Kolmer-Boerner serial dilution technic (*27*) was used throughout this study. The following procedure was employed: Dilutions of each agent were prepared separately. Equal quantities of the dilutions of each agent were combined and one ml. of the mixture was placed in a sterile tube. Nine ml. of nutrient broth were then added. The concentrations of agents resulting after the addition of the broth were reported as the final dilutions and are so recorded in all tables presented herein. Control tubes containing dilutions of each agent alone were also included. All tubes were inoculated with 0.1 ml. of a twenty-four hour culture of the test organism, incubated at 37° and observed at the end of five days. Six loopfuls of all tubes in which precipitation occurred were subcultured into 10 ml. of nutrient broth. The subcultures were incubated at 37° and observed at the end of two days. The nutrient broth consisted of:

Peptone (Armour)	10 Gm.
Beef Extract (Difco)	5 Gm.
Sodium chloride (reagent grade)	5 Gm.
Distilled water, q. s. to make 1000 ml.	

The pH was adjusted to 7.0 before sterilization in the autoclave at 121° C. (15 lb. pressure) for twenty minutes.

Three test organisms were employed in this investigation: *S. aureus* 209, *E. coli communis* and *Ps. aeruginosa.*

The surface active agents included in this study were:

1. Emulsept—a quaternary ammonium salt of the substituted pyridinium type (cationic-Emulsol Corp.)
2. BTC—a quaternary ammonium salt of the alkyl dimethyl benzyl ammonium chloride type (cationic—Onyx Chemical Co.).
3. Ceepryn—A quaternary ammonium compound of the alkyl pyridinium chloride type (cationic—Wm. B. Merrell Co.).
4. CTAB—a quaternary ammonium compound of the alkyl trimethyl ammonium bromide type (cationic—J. T. Baker Co.).
5. Isothan Q-15—a cationic surface active agent of the alkyl isoquinolinium type (Onyx Chem. Co.).
6. Duponol C—an anionic surface active agent of the sodium alkyl sulfate type (E. I. DuPont Nemours Co.).
7. Triton N-100—a non-ionic surface active agent of the polyethylether type (Rohm and Haas Co.).

One percent stock solutions (in water) of Emulsept, BTC, Ceepryn, CTAB, Isothan Q-15 and Duponol C were employed in making all dilutions. With Triton N-100, a ten percent stock solution in water was used.

Dilutions of 9-amino acridine hydrochloride were made from a 1:300 stock solution of the salt in distilled water (the maximum solubility of this compound). A one percent solution of cobalt chloride in distilled water ($CoCl_2.6H_2O$) was employed in making all dilutions of this substance.

Findings

A. *The effect of cobalt chloride on the bacteriostatic efficiencies of cationic and anionic surface active agents*

I. Combinations of cobalt chloride with each of the five cationic detergents, Emulsept, BTC, Isothan Q-15, Ceepryn and CTAB.

The findings obtained when these mixtures were tested against E. coli are reported in Table I. It will be noted that cobalt chloride solution, 1:2000, alone was bacteriostatic. The additions of cobalt chloride, 1:3000 and 1:5000, to solutions of four of the cationic agents (BTC, Isothan, Ceepryn and CTAB) increased the bacteriostatic efficiencies of the surface active agents. This was not observed with Emulsept-cobalt chloride combinations.

Mixtures of solutions of the cationic agents and cobalt chloride were tested against *Ps. aeruginosa.* The findings are recorded in

TABLE I

THE EFFECT OF COBALT CHLORIDE ON THE BACTERIOSTATIC EFFICIENCIES OF CATIONIC SURFACE ACTIVE AGENTS AGAINST E. COLI— OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Cationic Agent in Mixture				
		Emulsept	BTC	Isothan	Ceepryn	CTAB
1:20,000	cationic	—	—	—	—	—
1:30,000	"	+	—	—	—	+
1:40,000	"	+	+	—	—	+
1:50,000	"	+	+	—	+	+
1:60,000	"	+	+	+	+	+
1:20,000	cationic with 1:3000 cobalt chloride	—	—	—	—	—
1:30,000	"	+	—	—	—	—
1:40,000	"	+	—	—	—	—
1:60,000	"	+	—	—	—	—
1:80,000	"	+	—	—	—	—
1:100,000	"	+	+	—	—	+
1:120,000	"	+	+	+	+	+
1:20,000	cationic with 1:5000 cobalt chloride	—	—	—	—	—
1:40,000	"	+	—	—	—	+
1:60,000	"	+	+	—	—	+
1:80,000	"	+	+	—	—	+
1:100,000	"	+	+	+	+	+
1:2000	cobalt chloride	—	—	—	—	—
1:2500	" "	+	+	+	+	+

\+ growth
— no growth

Table II. In all tests, cobalt chloride solution, 1:2000, alone was bacteriostatic; the addition of cobalt chloride, 1:4000 and 1:6000, to solutions of the cationic agents, BTC and Isothan, resulted in a slight increase in efficiency.

In all tests employing *S. aureus*, the addition of cobalt chloride, 1:10,000 and 1:15,000, to solutions of the five cationic agents resulted in an increase of bacteriostatic activity except with Emulsept (see Table III). Cobalt chloride solution, 1:5000, was bacteriostatic.

TABLE II

THE EFFECT OF COBALT CHLORIDE ON THE BACTERIOSTATIC EFFICENCIES OF CATIONIC SURFACE ACTIVE AGENTS AGAINST Ps. AERUGINOSA— OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Cationic Agent in Mixture				
		Emulsept	BTC	Isothan	Ceepryn	CTAB
1:1000	cationic	—	—	—	+	+
1:2000	"	—	—	+	+	+
1:3000	"	—	—	+	+	+
1:4000	"	+	—	+	+	+
1:5000	"	+	+	+	+	+
1:2000	cationic with 1:4000 cobalt chloride	—	—	—	+	+
1:3000	"	—	—	—	+	+
1:4000	"	+	—	—	+	+
1:5000	"	+	—	—	+	+
1:6000	"	+	+	+	+	+
1:2000	cationic with 1:6000 cobalt chloride	—	—	—	+	+
1:3000	"	—	—	—	+	+
1:4000	"	+	—	+	+	+
1:5000	"	+	+	+	+	+
1:2000	cobalt chloride	—	—	—	—	—
1:3000	" "	+	+	+	+	+

+ growth
— no growth

II. Combinations of cobalt chloride with the anionic surface active agent, Duponol C.

The strongest solution of Duponol C employed (1:2000) did not display bacteriostatic activity against *E. coli* or *Ps. aeruginosa.*

TABLE III

THE EFFECT OF COBALT CHLORIDE ON THE BACTERIOSTATIC EFFICIENCIES OF CATIONIC SURFACE ACTIVE AGENTS AGAINST S. AUREUS—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Cationic Agent in Mixture				
		Emulsept	BTC	Isothan	Ceepryn	CTAB
1:100,000	cationic	—	—	—	—	—
1:200,000	"	+	—	—	—	—
1:300,000	"	+	—	—	—	—
1:400,000	"	+	—	—	—	—
1:500,000	"	+	+	—	+	+
1:600,000	"	+	+	+	+	+
1:700,000	"	+	+	+	+	+
1:100,000	cationic with 1:10,000 cobalt chloride	—	—	—	—	—
1:200,000	"	+	—	—	—	—
1:300,000	"	+	—	—	—	—
1:400,000	"	+	—	—	—	—
1:500,000	"	+	—	—	—	—
1:600,000	"	+	—	—	—	—
1:800,000	"	+	+	—	—	—
1:1,000,000	"	+	+	+	—	—
1:1,200,000	"	+	+	+	—	—
1:1,500,000	"	+	+	+	+	+
1:100,000	cationic with 1:15,000 cobalt chloride	—	—	—	—	—
1:200,000	"	+	—	—	—	—
1:400,000	"	+	—	—	—	—
1:600,000	"	+	—	—	—	—
1:800,000	"	+	+	+	+	+
1:1,000,000	"	+	+	+	+	+
1:5000	cobalt chloride	—	—	—	—	—
1:7000	" "	+	+	+	+	+

\+ growth
— no growth

Cobalt chloride solution, 1:2000, was bacteriostatic against both organisms. The addition of Duponol C solution, 1:5000, resulted in cobalt chloride solution, 1:3000, being effective against *E. coli* but mixtures of these two agents did not display an increase in efficiency against *Ps. aeruginosa* (Table IV).

The findings obtained with Duponol C-cobalt chloride mixtures against *S. aureus* are recorded in Table IV. An increase in bacteriostatic efficiency is apparent. When tested separately, cobalt chloride solution 1:5000, and Duponol C solution, 1:10,000 were inhibitory. In mixtures of the two agents, a solution of cobalt chloride, 1:15,000, with Duponol C, 1:30,000, was bacteriostatic.

TABLE IV

THE EFFECT OF AN ANIONIC SURFACE ACTIVE AGENT (DUPONOL C) ON THE BACTERIOSTATIC EFFICIENCY OF COBALT CHLORIDE AGAINST PS. AERUGINOSA, E. COLI AND S. AUREUS— OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		E. Coli	Ps. Aeruginosa	S. Aureus
1:2000	Duponol C	+	+	—
1:5000	"	+	+	—
1:10,000	"	+	+	—
1:20,000	"	+	+	+
1:25,000	"	+	+	+
1:2000	Duponol C with 1:3000 cobalt chloride	—	+	—
1:5000	"	—	+	—
1:10,000	"	+	+	—
1:2000	Duponol C with 1:5000 cobalt chloride	+	+	—
1:25,000	Duponol C with 1:15,000 cobalt chloride	+	+	—
1:30,000	"	+	+	—
1:35,000	"	+	+	+
1:40,000	"	+	+	+
1:2000	cobalt chloride	—	—	—
1:3000	" "	+	+	—
1:5000	" "	+	+	—
1:10,000	"	+	+	+

\+ growth
— no growth

B. The effect of 9-amino acridine on the bacteriostatic efficiencies of cationic and anionic surface active agents

I. Combinations of 9-amino acridine with the five cationic agents (Emulsept, BTC, Isothan Q-15, Ceepryn and CTAB)

Data obtained in tests on these mixtures against *E. coli* are recorded in Table V. The concentration of 9-amino acridine alone

TABLE V

THE EFFECT OF 9-AMINO ACRIDINE ON THE BACTERIOSTATIC EFFICIENCIES OF CATIONIC SURFACE ACTIVE AGENTS AGAINST E. COLI— OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Cationic Agent in Mixture				
		Emulsept	BTC	Isothan	Ceepryn	CTAB
1:20,000	cationic	—	—	—	—	—
1:30,000	"	+	—	—	—	—
1:40,000	"	+	+	—	—	—
1:50,000	"	+	+	—	—	+
1:60,000	"	+	+	+	+	+
1:50,000	cationic with 1:60,000 9-amino acridine	—	—	—	—	—
1:60,000	"	+	—	—	—	—
1:80,000	"	+	+	—	—	+
1:100,000	"	+	+	+	—	+
1:120,000	"	+	+	+	+	+
1:20,000	cationic with 1:80,000 9-amino acridine	—	—	—	—	—
1:30,000	"	—	—	—	—	—
1:40,000	"	+	—	—	—	—
1:50,000	"	+	+	—	—	+
1:60,000	"	+	+	—	—	+
1:80,000	"	+	+	+	—	+
1:100,000	"	+	+	+	+	+
1:20,000	9-amino acridine	—	—	—	—	—
1:30,000	"	+	+	+	+	+

+ growth
— no growth

which displayed bacteriostasis was 1:20,000. The addition of 9-amino acridine, 1:60,000 and 1:80,000, to solutions of the five cationic agents resulted in an increase in the bacteriostatic efficiencies of the surface active agents.

The findings obtained in tests on these combinations against *Ps. aeruginosa* are recorded in Table VI. Although 9-amino acridine solution, 1:3000, failed to inhibit the growth of the test organism, the addition of 1:6000 of this compound to solutions of three cationic agents (Emulsept, BTC, and Isothan) resulted in an increase in efficiency. Combinations of Ceepryn or CTAB with the acridine salt showed no potentiating effects.

When *S. aureus* was employed as the test organism, 9-amino acridine solution, 1:20,000, was inhibitory. The addition of 1:60,000 and 1:80,000 of the acridine salt to solutions of the five cationic agents resulted in an increase in efficiency in all cases (see Table VII).

TABLE VI

THE EFFECT OF 9-AMINO ACRIDINE ON THE BACTERIOSTATIC EFFICIENCIES OF CATIONIC SURFACE ACTIVE AGENTS AGAINST PS. AERUGINOSA— OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

		Cationic Agent in Mixture				
	Concentration	Emulsept	BTC	Isothan	Ceepryn	CTAB
1:1000	cationic	—	—	+	+	+
1:2000	"	+	—	+	+	+
1:3000	"	+	—	+	+	+
1:4000	"	+	+	+	+	+
1:5000	"	+	+	+	+	+
1:2000	cationic with 1:600 9-amino acridine	—	—	—	+	+
1:3000	"	—	—	—	+	+
1:4000	"	+	—	—	+	+
1:5000	"	+	—	+	+	+
1:6000	"	+	—	+	+	+
1:8000	"	+	+	+	+	+
1:3000	9-amino acridine*	+	+	+	+	+

* Maximum concentration possible with this technic

\+ growth

— no growth

II. Combinations of 9-amino acridine with the anionic surface active agent, Duponol C.

Combination of these two agents resulted in a precipitation similar to that produced on the admixture of solutions of a cationic and an anionic surface active agent. It is to be noted that the acridines act as cationic agents (28). The precipitate upon examination did not reveal bacteriostatic activity.

TABLE VII

THE EFFECT OF 9-AMINO ACRIDINE ON THE BACTERIOSTATIC EFFICIENCIES OF CATIONIC SURFACE ACTIVE AGENTS AGAINST S. AUREUS—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration	Cationic Agent in Mixture				
	Emulsept	BTC	Isothan	Ceepryn	CTAB
1:100,000 cationic	—	—	—	—	—
1:200,000 "	+	—	—	—	—
1:300,000 "	+	—	—	—	—
1:400,000 "	+	—	—	+	—
1:600,000 "	+	+	+	+	+
1:100,000 cationic with 1:60,000 9-amino acridine	—	—	—	—	—
1:200,000 "	—	—	—	—	—
1:300,000 "	+	—	—	—	—
1:400,000 "	+	—	—	—	—
1:600,000 "	+	—	—	+	—
1:800,000 "	+	—	—	+	+
1:1,000,000 "	+	—	—	+	+
1:1,200,000 "	+	+	+	+	+
1:1,400,000 "	+	+	+	+	+
1:100,000 cationic with 1:80,000 9-amino acridine	—	—	—	—	—
1:200,000 "	+	—	—	—	—
1:300,000 "	+	—	—	—	—
1:400,000 "	+	—	—	+	—
1:600,000 "	+	—	—	+	+
1:800,000 "	+	—	—	+	+
1:1,000,000 "	+	+	—	+	+
1:1,200,000 "	+	+	+	+	+
1:20,000 9-amino acridine	—	—	—	—	—
1:30,000 "	+	+	+	+	+

+ growth
— no growth

TABLE VIII

THE EFFECT OF A NON-IONIC SURFACE ACTIVE AGENT (TRITON N-100) ON THE BACTERIOSTATIC ACTIVITY OF CATIONIC AGENTS AGAINST E. COLI—OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration	Cationic Agent in Mixture				
	Emulsept	BTC	Isothan	Ceepryn	CTAB
1:10,000 cationic	—	—	—	—	—
1:20,000 "	—	—	—	—	—
1:30,000 "	+	—	—	—	—
1:40,000 "	+	+	—	—	+
1:50,000 "	+	+	—	+	+
1:60,000 "	+	+	+	+	+
1:2000 cationic with 1:200 Triton N-100	+	—	+	+	+
1:5000 "	+	+	+	+	+
1:10,000 "	+	+	+	+	+
1:2000 cationic with 1:500 Triton N-100	—	—	—	—	+
1:5000 "	+	—	+	+	+
1:10,000 "	+	+	+	+	+
1:2000 cationic with 1:1000 Triton N-100	—	—	—	—	—
1:5000 "	+	—	—	—	+
1:10,000 "	+	+	—	+	+
1:20,000 "	+	+	+	+	+
1:10,000 cationic with 1:5000 Triton N-100	—	—	—	—	—
1:20,000 "	—	—	—	—	+
1:30,000 "	+	+	—	+	+
1:50,000 "	+	+	+	+	+
1:10,000 cationic with 1:10,000 Triton N-100	—	—	—	—	—
1:20,000 "	—	—	—	—	—
1:30,000 "	+	+	—	+	+
1:50,000 "	+	+	+	+	+
1:10,000 cationic with 1:25,000 Triton N-100	—	—	—	—	—
1:20,000 "	—	—	—	—	—
1:30,000 "	+	—	—	—	—
1:50,000 "	+	+	+	+	+
1:200 Triton N-100	+	+	+	+	+

\+ growth
— no growth

TABLE IX

THE EFFECT OF A NON-IONIC AGENT (TRITON N-100) ON THE BACTERIOSTATIC ACTIVITIES OF CATIONIC SURFACE ACTIVE AGENTS AGAINST PS. AERUGINOSA— OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration	Cationic Agent in Mixture				
	Emulsept	Isothan	BTC	Ceepryn	CTAB
1:2000 cationic	—	+	—	+	+
1:3000 "	—	+	—	+	+
1:4000 "	—	+	—	+	+
1:5000 "	+	+	+	+	+
1:2000 cationic with 1:200 Triton N-100	+	+	+	+	+
1:3000 "	+	+	+	+	+
1:4000 "	+	+	+	+	+
1:5000 "	+	+	+	+	+
1:2000 cationic with 1:500 Triton N-100	+	+	+	+	+
1:3000 "	+	+	+	+	+
1:4000 "	+	+	+	+	+
1:5000 "	+	+	+	+	+
1:2000 cationic with 1:1000 Triton N-100	—	+	—	+	+
1:3000 "	+	+	+	+	+
1:4000 "	+	+	+	+	+
1:5000 "	+	+	+	+	+
1:2000 cationic with 1:5000 Triton N-100	—	+	—	+	+
1:3000 "	—	+	—	+	+
1:4000 "	+	+	+	+	+
1:5000 "	+	+	+	+	+
1:2000 cationic with 1:10,000 Triton N-100	—	+	—	+	+
1:3000 "	—	+	—	+	+
1:4000 "	—	+	—	+	+
1:5000 "	+	+	+	+	+
1:200 Triton N-100	+	+	+	+	

+ growth

— no growth

C. The effect of Triton N-100, a non-ionic surface active agent, on the bacteriostatic efficiencies of cationic and anionic surface active agents

I. Combinations of Triton N-100 with each of the five cationic agents, Emulsept, BTC, Isothan Q-15, Ceepryn and CTAB.

The admixture of Triton N-100 and solutions of these cationic agents resulted in a marked neutralization of the bacteriostatic activity of the latter against *E. coli* and *Ps. aeruginosa* (see Tables VIII and IX). The ratio of the non-ionic agent to the cationic agent in the mixture appeared to be a critical factor in this neutralization. In the case of *E. coli*, ratios of ten parts non-ionic to one part cationic prevented the bacteriostatic action of the latter in most cases. With the BTC-Triton N-100 mixtures, however, a ratio of twenty-five parts non-ionic to one part cationic was required. In tests employing *Ps. aeruginosa*, the same neutralization of bacteriostatic action occurred. However, smaller ratios of non-ionic to cationic were required (from 4:1 to 2:1). With both organisms, a smaller excess of non-ionic was necessary for neutralization as the concentration of the cationic agent in the mixture was progressively reduced.

With *S. aureus* as the test organism, the marked neutralization of the bacteriostatic activity of the five cationic agents by Triton N-100 did not occur (see Table X). In fact, a potentiation of the bacteriostatic activity of the cationic agents occurred in certain mixtures. With high concentrations of Triton N-100, little or no effect on the bacteriostatic activity of the cationic agents was noted, but at higher dilutions the potentiation noted above was apparent. The following will serve as an example: Ceepryn solution, 1:200,000, was bacteriostatic against *S. aureus* after five days incubation. A solution containing Ceepryn at a concentration of 1:500,000 with Triton N-100, 1:200, was inhibitory during the same period of time. As the concentration of Triton in the mixture was made progressively weaker, the increase in bacteriostatic efficiency became stronger. The peak of the increase was reached in solutions containing Triton, 1:5000, with Ceepryn, 1:1,500,000.

High concentrations of Triton (1:200) had no bacteriostatic activity against any of the test organisms.

TABLE X

THE EFFECT OF A NON-IONIC SURFACE ACTIVE AGENT (TRITON N-100) ON THE BACTERIOSTATIC EFFICIENCIES OF CATIONIC AGENTS AGAINST S. AUREUS—
OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Cationic Agent in Mixture				
		Emulsept	BTC	Isothan	Ceepryn	CTAB
1 :100,000	cationic	—	—	—	—	—
1 :200,000	"	+	—	—	—	—
1 :300,000	"	+	—	—	+	—
1 :400,000	"	+	—	—	+	+
1 :500,000	"	+	—	—	+	+
1 :600,000	"	+	+	—	+	+
1 :700,000	"	+	+	+	+	+
1 :100,000	cationic with 1 :200 Triton N-100	+	—	—	—	—
1 :300,000	"	+	—	—	—	—
1 :500,000	"	+	+	—	—	—
1 :700,000	"	+	+	+	+	+
1 :100,000	cationic with 1 :500 Triton N-100	—	—	—	—	—
1 :300,000	"	+	—	—	—	—
1 :500,000	"	+	—	—	—	—
1 :700,000	"	+	—	+	—	—
1 :1,000,000	"	+	—	+	—	—
1 :1,500,000	"	+	+	+	—	—
1 :2,000,000	"	+	+	+	+	+
1 :300,000	cationic with 1 :1000 Triton N-100	—	—	—	—	—
1 :500,000	"	+	—	—	—	—
1 :700,000	"	+	—	—	—	—
1 :1,000,000	"	+	—	—	—	—
1 :2,000,000	"	+	—	—	+	+
1 :3,000,000	"	+	+	+	+	+
1 :1,000,000	cationic with 1 :5000 Triton N-100	—	—	—	—	—
1 :1,500,000	"	+	—	—	—	—
1 :2,000,000	"	+	—	—	+	+
1 :3,000,000	"	+	+	+	+	+
1 :700,000	cationic with 1 :10 000 Triton N-100	—	—	—	—	—
1 :1,000,000	"	+	—	—	+	—
1 :1,500,000	"	+	—	+	+	—
1 :2,000,000	"	+	—	+	+	+
1 :100,000	cationic with 1 :25,000 Triton N-100	—	—	—	—	—
1 :300,000	"	+	—	—	—	—
1 :500,000	"	+	—	—	+	—
1 :700,000	"	+	+	—	+	+
1 :1,000,000	"	+	+	+	+	+
1 :100,000	cationic with 1 :50,000 Triton N-100	—	—	—	—	—
1 :300,000	"	+	—	—	+	—
1 :500,000	"	+	—	—	+	+
1 :700 000	"	+	+	+	+	+
1 :200	Triton N-100	+	+	+	+	+

+ growth
—no growth

II. Combinations of Triton N-100, a non-ionic surface active agent, with the anionic detergent, Duponol C.

With *S. aureus* as the test organism, the addition of Triton N-100 to solutions of Duponol C resulted in a neutralization of the bacteriostatic activity of the latter (see Table XI). This neutralization was similar to that occurring when mixtures of the non-ionic and cationic agents were tested against *E. coli* and *Ps. aeruginosa*. With the Triton-Duponol mixtures against *S. aureus*, however, an excess of the non-ionic agent was not necessary for neutralization. It will be noted in Table XI that Duponol C solution, 1:5000, was bacteriostatic against S. aureus after five days incubation. The addition of Triton N-100, 1:10,000, to Duponol C solution, 1:5000, neutralized the anionic agent and allowed the organism to grow in such a mixture. Growth also occurred in a mixture containing Triton N-100, 1:5000, and Duponol C, 1:3000, even though Duponol C alone at a concentration of 1:5000 was bacteriostatic.

TABLE XI

THE EFFECT OF A NON-IONIC SURFACE ACTIVE AGENT (TRITON N-100) ON THE BACTERIOSTATIC EFFICIENCY OF AN ANIONIC SURFACE ACTIVE AGENT (DUPONOL C) AGAINST S. AUREUS— OBSERVATIONS MADE AFTER FIVE DAYS INCUBATION AT 37° C.

Concentration		Growth
1:2000	Duponol	—
1:5000	"	—
1:10,000	"	+
1:2000	Duponol with 1:200 Triton N-100	+
1:3000	"	+
1:5000	"	+
1:2000	Duponol with 1:500 Triton N-100	+
1:3000	"	+
1:5000	"	+
1:2000	Duponol with 1:1000 Triton N-100	+
1:3000	"	+
1:5000	"	+
1:2000	Duponol with 1:5000 Triton N-100	—
1:3000	"	+
1:5000	"	+
1:2000	Duponol with 1:10,000 Triton N-100	—
1:3000	"	—
1:5000	"	+
1:2000	Duponol with 1:25,000 Triton N-100	—
1:3000	"	—
1:5000	"	—
1:10,000	"	+
1:200	Triton N. 100	+

Strong concentrations of Triton N-100 (1:200) and Duponol C (1:2000), alone and in combination, had no bacteriostatic activity against *E. coli* and *Ps. aeruginosa.*

Solutions of all agents remained stable over the period of time they were employed. Stock solutions up to five months of age were used with no evidence of deterioration in bacteriostatic efficiency.

Summary

The effects of cobalt chloride, 9-amino acridine and a non-ionic surface active agent (Triton N-100) on the bacteriostatic properties of five cationic surface active agents (Emulsept, BTC, Isothan Q-15, Ceepryn and CTAB) and of one anionic surface active agent (Duponol C) were investigated using a modification of the Kolmer-Boerner serial dilution technic.

Conclusions

The effect of cobalt chloride on the bacteriostatic activities of five cationic surface active agents (Emulsept, BTC, Isothan Q-15, Ceepryn and CTAB) and one anionic surface active agent (Duponol C) varied with the particular substance. All of the agents except Emulsept showed increases in bacteriostatic efficiences when mixed with the cobalt salt and tested against *E. coli* and *S. aureus.* In tests employing *Ps. aeruginosa,* only two of the six surface active agents displayed increases in bacteriostatic activity (BTC and Isothan Q-15).

Variable results were also obtained with mixtures of 9-amino acridine and the same surface active agents. All combinations of 9-amino acridine and the five cationic agents gave increases in bacteriostatic efficiences when tested against *E. coli* and *S. aureus.* In tests employing *Ps. aeruginosa,* Emulsept, BTC and Isothan Q-15 showed increases in efficiencies. The admixture of 9-amino acridine with Duponol C resulted in a precipitate; the mixture did not display bacteriostatic properties.

The bacteriostatic activity of the five cationic agents against *E. coli* and *Ps. aeruginosa* was neutralized by suitable excesses of the non-ionic agent, Triton N-100. Ratios of ten parts non-ionic agent to one part cationic detergent were sufficient for neutralization against *E. coli.* In test employing *Ps. aeruginosa,* a ratio of three parts Triton N-100 to one part cationic agent resulted in neutralization.

The effect of Triton N-100 on the bacteriostatic activity of the five cationic agents against *S. aureus* varied with the concentration of non-ionic present. With high concentrations of Triton N-100, little or no effect on the bacteriostatic efficiencies of the cationic agents was noted. As the concentration of the non-ionic was progressively reduced, a marked increase in bacteriostatic efficiencies of the five cationic agents resulted.

The bacteriostatic action of the anionic surface active agent, Duponol C, against *S. aureus* was neutralized by the non-ionic agent, Triton N-100. No excess of the non-ionic agent was required for this neutralization.

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Lactobacillus Acidophilus Counts Reduced by Chlorophyll-Containing Oral Hygiene Products. G. W. Rapp. International Assoc. For Dental Research. June 24, 1949. A quantitative relationship has been shown to exist between the bacterial count of *Lactobacillus Acidophilus* and the incidence of dental caries. However, it has not been shown definitely that this organism is the cause of dental decay.

Dr. Rapp reported the results of a study made upon volunteers using the bacterial count as an indication of the effectiveness of chlorophyll-containing preparations in controlling dental caries. The volunteers were tested weekly for a period of 6 weeks to determine their normal bacterial counts. Fifty subjects were then given a chlorophyll-containing toothpaste and instructed to use it twice a day, once to be following breakfast. A second group of 35 subjects were given an ordinary toothpaste and a month wash containing chlorophyll. This group received the same instructions except that brushing of the teeth was to be followed by a rinse with the mouth wash. A control group of 15 subjects were instructed to use their regular oral hygiene procedure. Salivary bacterial counts were then taken at an interval of 10 days, 4 weeks, and then every 2 weeks until the 26-week study period had elapsed.

Ninety per cent of the subjects using the chlorophyll-containing toothpaste were negative for *Lactobacillus Acidophilus* by the end of the 26-week study period. Many had been negative for some time, in fact, 26 per cent were negative within 10 days. Comparable results were obtained in the group using the ordinary toothpaste and the chlorophyll-containing mouth wash. This indicated that brushing with the chlorophyll was not necessary in order to obtain good results. The control group showed considerable fluctuation in bacterial counts but no material reduction. The author therefore concluded that chlorophyll may be a means of preventing or at least reducing the incidence of dental caries when used in oral hygiene.

HANSEN'S DISEASE

By Leonard D. Frescoln, M. D.*

ALTHOUGH leprosy is not endemic in this Country and a new case may be seen here only occasionally it is important that physicians consider it in their differential diagnoses. Establishment of the diagnosis is usually not difficult, once the disease is suspected. A brief review of the subject of leprosy including treatment and management is, therefore, presented. There are possibly some five million cases of leprosy in the world, with perhaps 1500 cases in the U. S. Possessions, many for a long time undiagnosed. The disease prevails especially in the humid climate of the tropics and particularly under unsanitary conditions.

In the recorded Bible references to the disease, the ceremonial cleansing required of unclean skin eruptions such as syphilis, psoriasis, dermatitis, leprosy (zaraath, Hebrew meaning blemish, and lepra meaning scaly) led to the fear of transmission of such diseases as seen in Palestine.

In 1874, Dr. Gerhard Armauer Hansen of Norway found Leprosy to be caused by the *Mycobacterium lepra*, a small beaded acid fast rod, found in parallel groups and in a degenerated cell called Globus (1). The organisms are found in the nasal discharge, beaded nerves, skin surface open lesions and nodules. In an exacerbation of the disease a fibroid swelling of collagen may appear in the lepromatous nodules causing fever and pain. In order to dispel the stigma connoted by the term "Leprosy" an effort is being made to call the disease "Hansen's Disease".

The mode of transmission of the disease is not definitely known and efforts to transmit it experimentally have failed; however, its transmission is enhanced by warm climates and unsanitary surroundings, particularly to children and young adults. The length of time from exposure to the appearance of lesions may be ten years or more. In addition to its difficulty of acquirement its course is most chronic. Patients not responding to treatment may die in 9 or 10 years.

During the 52 years existence of the Leprosarium at Carville, Louisiana, now the United States Marine Hospital under Dr. Johan-

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sen, never has a doctor or nurse contracted the disease. The usual precautions of washing hands with soap and water, use of rubber gloves and gowns in treating and dressing cases are observed.

There are two principal forms of the disease, the lepromatous (2) type characterized by skin tubercle (over 50%) which is bacteriologically positive, and the neuro-erythematous (3) or tuberculoid type with anesthetic areas which is bacteriologically negative. There are also mixed forms and the so-called Lacerine type characterized by small infarcts. Leprosy has been mistaken for syphilis, tuberculosis, scleroderma, vitiligo, allergy, malnutrition, dermatitis, yaws, leucoderma, "cosmetic" rash, psoriasis, avitaminosis, tinea, leishmaniasis, lupus, injuries of various sorts and pellagra. Complications include neuritis, irido-cyclitis, blindness, osteomyelitis, bone cyst, arthritis and associated tuberculosis, fractures and nephritis, although the viscera are not involved specifically in the disease. There is present, fever at times, weakness, loss of weight, itching and pain. Some nodular forms have marked creases in the face, giving the "Visage leonine". In

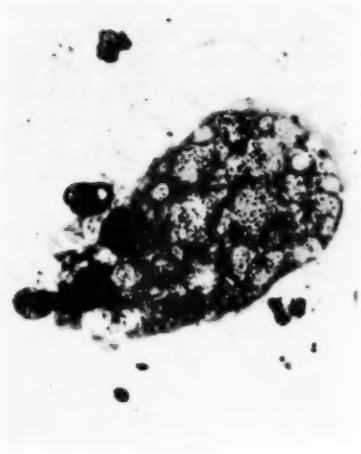

FIGURE 1
M. leprae IN NODULE

FIGURE 2
NODULAR CASE
(Municipal Hospital)

the anaesthetic variety there is loss of sensation of touch, pain and temperature. Trophic disturbances such as ulcers, bone and joint involvement and amputations, occur. The ulnar nerve especially may give palpable nodular thickening with accompanying atrophies, as also may the peroneal, radial and facial nerves. Alopecia and anidrosis may accompany the disease. Occasionally there is paralysis of the throat muscles, aphonia and complete blindness. Depigmentations, contractures and claw hand occur. Because of insensibility to pain, injuries and burns often occur. Biopsies taken from tubercles and nerves help in making the diagnosis, as well as smears from the nasal mucosa and tissue juice especially in consideration of possible exposure to the disease.

X-rays of the digits will show demineralization in over 60% of cases, and especially in the heads of the metatarsals. There is seen also atrophy at the base of the phalanges of the toes and terminal phalanges of the digits of the hands (4), these all being pressure points. There may be cystic degeneration in the head of a metatarsal, containing the organism. Sometimes the very thin bone will fracture. Cyst of the head of the talus with shortening has been seen; also, enlargement of the nutrient foramina is common. Loss of digits (3) from bone absorption occurs.

Treatment consists of rest in bed in the early stages and isolation during the period of transmissibility, fresh air, good food and, as advanced by Dr. Faget of Carville and others, administration of the sulfa drugs, especially Promin, Diasone or Promizole. It is thought that the sulfones act upon the fatty capsule of the bacillus to destroy the germ. Other drugs used include Sulphetrone, chaulmoogra oil, Pyricidin, Promocetin and Rongalite. For painful areas and neuritis, Nupercaine ointment is applied, as also intragluteal injections of Fuadin and intravenous injections of calcium gluconate. For treatment of ulcers, surgical dressings, contrast baths, dyes, carbolized ointment, or sprays of 2% alcoholic solution of Tyrothricin are used. A 5% emulsion of Promin is used as a nasal spray and 40% ointment about the eyes.

The scleroderma may be treated with dihydrotachysterol and also Promin jelly. Associated pulmonary tuberculosis and psychosis are treated in the usual manner. Resultant anemia is treated by the use of iron and liver. In handling and dressing cases, precautions are taken on the part of attendants by use of carbolized soap and

water, and wearing surgical gloves. Physical therapy measures and occupational therapy are employed at the Leprosarium at Carville. Some of the convalescents are employed as orderlies and in the printing shop, clock repairing, seamstresses and pressing work.

Recreational activities include movies, dancing, baseball, golf and other games; religious guidance also is stressed. Sanitary laws should be enforced particularly in climates where the disease flourishes, especially as there is no known immunization for Leprosy.

Bone involvement generally begins in an anesthetic area which is traumatized then followed by secondary infection, trophic ulcer and necrosis of bone. Conservative surgical measures are used such as local antiseptic baths, antiseptic dressings and adequate dosage of Promin. Necrosis is likely to start at the terminal phalanges and, if not arrested, may result in amputation. There may occur a perforating ulcer of the foot with thinning of the metatarsals and possible osteomyelitis together with arthritis. There is a high percentage of such cases in India and Africa in regions where shoes are not worn. About 10 to 15% of advanced tuberculoid cases have ended in bone involvement and amputation of various parts; marked reduction of such involvement has resulted from modern treatment. Necrosed bone must be removed, soft tissues at times excised, wounds closed, sometimes skin-grafting done and parts put up in Plaster of Paris for 3 months. Crude streptomycin or a powdered preparation worked up into an ointment has been used for the deep perforating ulcer of the foot, trimming the edges and keeping the patient off his feet. When up, anterior pads may need to be placed in the shoes. The removal of the pressure on the part encourages healing of perforating ulcers.

Neglected cases may die within the first decade of the disease; fortunately, occasionally a case will be spontaneously cured.

The U. S. Public Health Service prescribes isolation of bacteriologically positive cases at the National Leprosarium until arrested, for six months, with negative reports, and then examination every six months, as well as all contacts, for a period of five years. In these days of world-wide transportation, the risk of spreading leprosy and other diseases is increased.

Courses in Tropical Medicine should be given more stress in our medical schools to make physicians better acquainted with leprosy and other tropical diseases.

Under U. S. Section 23 in the International List of Causes of Death, Leprosy in 1946 (and 1945) is listed as follows:

	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
New Cases ...	2	2	2	7	6	5	6	2	4	1	1	5	43
Deaths	1	3	1	2	3	1	0	1	1	1	0	1	15

New Cases ... 46 in 1945
Deaths ..... 26 in 1945

	N. Y. City	Ohio	Ill.	Md.	Fla.	La.	Texas	Colo.	Wash.	Cal.
New Cases ...	5 (2 in 1945)	0	1	2	8	10	2	1	1	7
Deaths	4 (0 in 1945)	1	0	0	0	7	3	0	0	2

In the Possessions	Hawaii	Panama	Puerto Rico	Virgin Islands
New Cases	33 (0 in '45)	14 (0 in '45)	5 (10 in '45)	1 (2 in '45)
Deaths	35 (31 in '45)	4 (4 in '45)	8 (9 in '45)	3 (2 in '45)

New York City has had 131 cases since 1928; of these, 57 were of the anesthetic type, there was some involvement of digits and amputation in 4 cases. (Department of Health, New York City, 1948.)

Some case histories of patients coming to the Philadelphia Hospital for Contagious Diseases are added, showing the temporary care of such patients in the past:

I. M., Mohammedan seaman from India. Numbness of forearms and lower extremities; violaceous areas on trunk and extremities. Subcutaneous nodes 2 x 4 cm. on forearms and neck. Right hand—atrophy of interossei; weakness of right foot. Right ulnar, median and peroneal nerves palpable. R. B. C.—5,200,000. Negative for lues. *Long bones demineralized.* Biopsy from neck swelling—vascular and inflammatory cytoplasm with cells suspicious of leprosy. Nasal smears showed 2 positive bacilli. Given alum precipitated diphtheria toxoid (Dr. Collier's method). Aspirin, phenobarbital, morphine were given to control pain. Iodomine, hot compresses, gentian violet, laxatives, forced fluids, cod liver oil, yeast, and orange juice made up the treatment. Case in 1 year deported to England.

T. M., Chinese, steamship fireman, 27 years of age, admitted 4-30-41 with burning of left upper eyelid, multiple nodules 1 mm. to 5 cm. in diameter over body, pain and partial anesthesia of face,

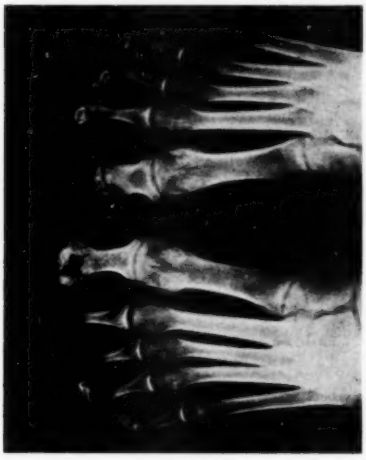

FIGURE 3
PHILIPPINO CASE
(Univ. of Penna. Hospital)

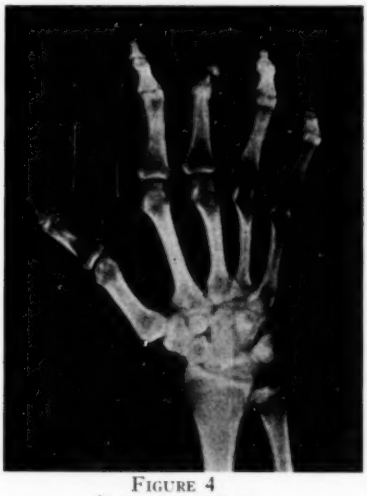

FIGURE 4
PHILIPPINO CASE
(Univ. of Penna. Hospital)

atrophic and anaesthetic areas of arms and front of lower extremities, post-cervical adenopathy, mucoid nasal discharge containing a few intracellular *M. lepra* bacilli; serosanguinous discharge from left ear with perforated drum. Tender calves and sciatic nerves with involvement of sensory and motor distribution of 5th lumbar and 1st sacral. Paralysis of flexors and extensors of left foot. Temperature 101° F., pulse 120. Blood negative for syphilis. Schick test negative. Section of skin and subcutaneous tissue showed in corium hyalinized fibrous tissue, macrophages, 2 areas of fibroblastic proliferation with plasma cells, vacuolated and destroyed cells, lymphocytes, numerous extracellular acid-fast rods, many of them granular. Low hemoglobin. Diagnosis: Active Mixed Leprosy. Given diphtheria toxoid. Deported 6-21-44.

E. J., from Panama, white, 22 years. Arrived 6 months previous to admission. Went to a Costa Rica school. Admitted 7-8-35. Cervical and inguinal adenitis. Bilateral claw hands, wasting of muscles during past 4 years. No sensation to heat. Pains on left side of face, elbows and uterus for a long time. Nasal discharge 7-8-35 negative, and on subsequent examinations. Purulent eruption of fingers and toes. Paralysis upper part of face; ulnar nerve nodular. All 3 nerves of hand involved. Anethesia amputation of right 1st and 2nd fingers and beginning on left hand. Loss of pain, touch and vibration sensation. Moderate left foot drop. Abdominal reflex absent. Periarthritis, phalangeal joints of hands and at heads of metacarpals with destruction of former. X-ray showed absence of joint spaces. Nails atrophied. Knee jerks 2 plus. Stiff flexion of terminal and middle phalanges and extension of first. Had injections for malaria, followed by abscesses. 8.6% eosinophiles, 45% lymphocytes, anisocytosis. No fragility of erythrocytes. Stools and urine negative for *M. lepra* Bacillus, as also section about ulnar nerve (hyperplastic thickening of vessels). Wassermann 2 plus. Given neoarsphenamine, insulin, Chaulmoogra oil. On discharge suspected atrophic arthritis.

G. A., 45, Philippino. Was in two leper colonies with aunt, a missionary. In 1919 at leper colony off Massachusetts, and 1 year later at Louisiana. Eloped in 1923. Small nodules resembling vaccination areas on upper extremities, abdomen, legs, dorsum of feet. High red count, lymphocytes 38%. *M. lepra* Bacillus negative on 5 examinations. Given chaulmoogra oil. Discharged 11-26-38 as arrested nodular leprosy.

F. C., 48, Chinese Chef, admitted 3-25-36. Right leg, face and right hand atrophied for about 1 year. Exposed in China apparently 15 years before. Right leg showed patches anaesthetic to pain, touch. Difficulty in walking because of right foot drop. Reflexes plus. Twitchings. Retention of urine. Urine, nose, tonsils, negative for *M. lepra* Bacillus on 5 occasions. Blood also negative. Chaulmoogra oil daily. Transferred to Philadelphia General Hospital 11-9-36 because of catatonic psychosis.

E. P., 34, Italian, sent from Graduate Hospital. Disease dates from October, 1934. Right face, left leg and forearm anaesthetic. Left claw-hand with atrophy. Ulnar nerves showed a granuloma. Nasal secretion negative. Caseous nodule on finger and small cyst on neck negative for *M. lepra* Bacillus also. Apparently exposed at Buenos Aires 15 years previously. Placed on chaulmoogra oil therapy. Eloped 5-28-36.

H. S., 57, Black, U. S. gardener. Nodular case with leonine appearance. Face, feet and left arm involved. Ulcerated septum. Conjunctivitis. Legs showed impaired sensation. Nose and throat examinations positive for *M. lepra* Bacillus. Mercury succinamide, influenza vaccine M. V. Discharged to U. S. Public Health Service.

J. B., 64, Russian woman. Nodular appearance of 5 years duration. Admitted 10-25-48 from University of Pennsylvania Hospital. Extensor surfaces of extremities, back, face, involved. Tender sciatic nerves. Chaulmoogra oil, influenza vaccine M. V. hypo, and Mercury succinamide intramuscularly.

A. G., Italian woman. Father died of paralysis. Leprosy for 16 years; in Louisiana until September, 1932. Coryza, falling out of eyebrows, leonine appearance. Infected tonsils. Smears from mucous membranes at first negative, then positive. Healed nodules. Given chaulmoogra oil treatments. Sent to Carville 9-22-33.

A. G., from Greece. Lepromatous variety, with considerable involvement of face. Smears from nasal discharge positive. (Had a tuberculous kidney removed.) Was on Streptomycin and Diasone with apparently no improvement. Now on Promin. Associated minimal pulmonary tuberculosis and tuberculosis of kidney.

F. B., from Philippines, recently entering United States. Diagnosed at University of Pennsylvania Hospital. Anaesthesia of legs and feet. Trophic ulcer on left great toe and scar of leg from treatment burn. Sections of ulnar nerve suggestion of leprosy. Returned to Philippines.

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Thyrotoxic Auricular Fibrillation Treated With Thiouracil. J. F. Goodwin. *Brit. Med. J.* No. 4611:895 (1949). Thiouracil and its compounds have been shown to be effective in causing reversion to sinus rhythm in cases of thyrotoxic auricular fibrillation. In this study 26 patients under treatment for thyrotoxicosis were found to have auricular fibrillation. All had been treated with thiouracil, methyl thiouracil or propyl thiouracil for a period not longer than 2 years. There was no clinical evidence of cardiovascular disease aside from the 11 patients who had a systolic blood pressure of 160 mm. of Hg. or greater. The average amount of the drug administered was 50 mg. a day. The duration of treatment varied from one week to 2 years.

All of the patients in this group were controlled as to the thyrotoxicosis and about 50 per cent showed a reversion to sinus rhythm. The author pointed out that a reversion to sinus rhythm is not an indication of the control of the thyrotoxicosis but none of the patients showed reversion to sinus rhythm unless the disease was controlled. In 13 of the patients electrocardiograms suggested associated cardiovascular disease. No superiority in the ability to abolish fibrillation was noted in any one of the three compounds used.

The author suggested that if fibrillation is not controlled within about 4 months of therapy other measures should be taken, such as the administration of quinidine.

THE INDUSTRIAL ALCOHOL PICTURE

By T. Swann Harding

IN prewar days the U. S. produced 200 million wine gallons of alcohol (95 percent purity), of which 85 million gallons were beverage alcohol and were consumed as potable spirits. Of the total, 100 million gallons were produced as industrial alcohol and were used for commercial, scientific, and medical purposes. The remaining 15 million gallons were produced as industrial alcohol but were actually used in the main for beverage blending. This alcohol was principally produced from grain and has today been largely replaced by potato alcohol.

Our entire prewar production of 200 million wine gallons of alcohol would have required the use of about 60 million bushels of corn, *had it all been made from corn.* This would have amounted to only 2½ percent of our annual corn crop but, in actuality, only 10-35 million gallons of alcohol were so produced. In 1947, we produced 74 million gallons from corn, mostly for beverage purposes. But, though 3 to 9 percent of our total alcohol production has customarily been produced from grain, its price is today too high to encourage its extended utilization for that purpose.

In prewar times 68 percent of our industrial alcohol was produced from imported molasses, and an additional 34 percent was synthetically derived from petroleum. During World War II our annual production of alcohol increased to 580 million gallons, and we had to turn to beverage distilling plants for their help. More grain was used for alcohol making than hitherto, in part to replace molasses which was less available during wartime. During the war our production of synthetic alcohol from petroleum increased to 60 million gallons a year, from a prewar average of about 25, and plants now or soon to be in operation should step this up to 75-100 million gallons.

This is about as much alcohol as was used for power production during the war. If, as claimed, synthetic alcohol can be produced at costs below that of producing it from raw materials other

than petroleum, such production may become quite an item as compared with the use of grain, or even of molasses. But synthetic alcohol plants are much more expensive to build and equip than fermentation plants, so production costs for alcohol from other raw materials may make the fermentation process cheaper. There are also other possibilities.

During the war the supply of alcohol was chronically below demand, hence price was no object. However, our peacetime production of alcohol has been traditionally based on the use of cheap raw materials.

Alcohol can be produced from sulfite liquor by fermentation and at approximately the cost of its production from grain. Furthermore, there is sufficient sulfite liquor to justify heavy expansion in this direction. Wood sources also exist in this country from which large quantities of alcohol can be derived, once certain mechanical and economic obstacles are overcome. Again, various agricultural residues, notably corncobs, offer possibilities, and the Department of Agriculture's Northern Research Laboratory at Peoria is trying these processes out in a large test plant.

A new future source of synthetic alcohol is via the Fischer-Tropsch process for the production of synthetic gasoline from natural gas or coal, and some 30 million gallons should be derived from plants now building or projected. Further expansion here would undoubtedly impinge heavily on the production of alcohol by fermentation processes.

Moreover much alcohol now used industrially goes into the production of acetic acid and esters, but these can be produced directly from ethylene or natural gas, without going through the alcohol stage, and by plants now in operation. Then isopropyl and methyl alcohol, both produced synthetically, are already replacing ethyl alcohol for many purposes, and can replace it for still more, thus contracting demand, for their production can readily be increased.

However, the production of alcohol from molasses is on the way back. But the over-all outlook for production from grain is bad at the moment. During World War II grain sprang into heavy

use because we had to have alcohol in huge quantities to produce synthetic rubber. We needed 330 million gallons of alcohol a year for this purpose alone, at peak. But even then *more wheat and grain sorghums than corn* were used as raw materials, and peacetime synthetic rubber production can be expected to absorb little grain.

Of course, the more effective recovery and utilization of the byproducts from grain fermentation will help this industry. Furthermore the increased use of alcohol in motor fuel has very interesting possibilities. For one thing our supply of petroleum is definitely limited. But fuel alcohol can be produced almost at will from air, water, sunshine, and soil, without significant drain upon natural resources, save to some extent upon potassium, phosphorus, and nitrogen.

Finally, this thought is arresting. The production from coal of the 5 million barrels of oil we now use daily, via the Fischer-Tropsch process would require that we mine twice as much coal as the total mined in 1941. That would mean trebling our output of coal and an investment of twenty-five billion dollars besides. No wonder the Department of Agriculture is so seriously interested in the production of fuel alcohol from agricultural residues by some new fermentation processes and the recovery and utilization of the byproducts of this process.

The following developments have great significance in this connection:

(1) Blending 1 gallon of ethyl alcohol and 9 gallons of low-grade gasoline will make 10 gallons of premium grade antiknock motor fuel.

(2) Using a small gadget that automatically injects a mixture of alcohol and water into the engine when it is under heavy load will let a truck driver take the hills in high instead of at 5 miles an hour.

(3) For passenger cars, the adoption of engine devices already available, would enable drivers to get a similar advantage from alcohol-water injection while using low-octane gasoline as the principal fuel.

(4) Development at the Northern Regional Research Laboratory of fungal amylase as a substitute for malt in manufacture of alcohol from grain reduces the cost of alcohol by about 3 cents a gallon.

(5) Progress has been made in development of economies in the process for manufacturing alcohol from farm wastes such as corncobs, and tests are now under way on a semi-commercial scale.

Phosphorus Is Found as Element in Vitamin B_{12}. B. Ellis, V. Petrow, and G. F. Snook. *J. Pharmacy and Pharmacol. 1:*287 (1949). Paper strip chromatograms revealed the presence of phosphate on them during a study of the composition of vitamin B_{12}. Hydrochloric acid hydrolysates were used in the study. These hydrolysates were deeply colored from a pigmented cobalt-containing fragment of the vitamin molecule. The problem which the investigators attempted to resolve was to find a quantitative method for the separation of the phosphate ion from the pigmented material.

A method which was finally developed involved spotting the vitamin B_{12} hydrolysate on strips of filter paper, irrigating with isobutyric acid, locating phosphate on the guide strips by means of the ammonium molybdate and benzidine spot test reagents, and then estimating the phosphate colorimetrically after elution from the paper. In order to liberate the inorganic phosphorus from the molecule the hydrochloric acid had to be heated at 100 C. with the vitamin. In the development of the color the maximum intensity was developed in 20 minutes and then measured with a "Spekker" photoelectric absorptiometer.

The results of the assay method revealed that the phosphorus content was 2.1 per cent as compared with 4.0 per cent of cobalt. This gives an atomic ratio of 1:1 for phosphorus and cobalt in the molecule of vitamin B_{12}.

GLYCERINE AND THE VITAMINS

By Milton A. Lesser

IN the recently published prescription survey—the one conducted by the American Council on Education—thiamin hydrochloride and riboflavin held positions one and two, respectively, on the basis of frequency of use. Closely following, in position number four, was glycerine. It may be a coincidence that glycerine is so closely associated with the vitamins on this list, but it is a fact that glycerine has found frequent and growing use in the formulation of vitamin products.

Aside from pointing to the new importance of the B vitamins, this survey (1) served to reaffirm the importance of glycerine as a prescription ingredient. Such a conclusion is all the more impressive in view of the broad scope of the survey, which analyzed 13,125 prescriptions collected in November 1946 or shortly thereafter from pharmacists in 186 villages, towns and cities, distributed throughout 39 states and representing 220 pharmacies. Glycerine earned "frequency rank" number four because it was used 1,100 times in these prescriptions. By itself, it occurred 128 times, and 972 times as a prescription ingredient.

These figures serve to reflect the adaptability of glycerine as a member of the medical armamentarium. Its wide usefulness is a reflection of its rare combination of physical properties. Because of these properties it may serve as a hygroscopic agent or humectant, as a solvent, suspending and bodying agent, as a sweetener, and as an antifreeze. This last looms important with vitamin preparations because they are kept in refrigerators.

These qualities are called in to play not only in the preparation of commercial vitamin products, but also in many of the items compounded by the pharmacist himself. They are rather extensively utilized in preparations containing individual or multiple members of the vitamin B complex. For example, one proprietary Thiamin

Chloride Elixir, for use in the prevention and treatment of conditions associated with vitamin B deficiency, is described as containing, per fluid ounce, 10 mg. of thiamin chloride in a vehicle of sherry wine and glycerine.

A similar preparation, incorporating a number of the B vitamins, has been given in the "New Jersey Formulary" (2). This Elixir of Vitamin B Preparation (N. J. F.) is made from:

Liver B vitamins concentrate, U. S. P.	22.5 Gm.
Benzoic acid	0.5 Gm.
Citric acid	0.4 Gm.
Syrup	80.0 cc.
Glycerine	55.0 cc.
Sherry wine, to make	500.0 cc.

Mix these ingredients, macerate for 24 hours with occasional shaking. Filter clear. Then add the following:

Thiamin hydrochloride	0.050 Gm.
Riboflavin	0.020 Gm.
Pyridoxine hydrochloride	0.025 Gm.
Nicotinic acid	0.200 Gm.

Each fluid ounce of the elixir contains 3 mg. of thiamine hydrochloride, 1.2 mg. of riboflavin, 12 mg. of nicotinic acid, and 1.6 mg. pyridoxine hydrochloride, plus the fractions of riboflavin and nicotinic acid, including 17 mg. of choline in the liver concentrate. These are combined in a pleasantly flavored vehicle.

Of kindred interest is the stable, pleasingly colored and quite palatable raspberry elixir described by Kendall (3), and designed as an appealing vehicle for B complex vitamins. This elixir contains:

Benzoic acid	1 Gm.
Tincture cardamom compound	5 cc.
Alcohol	150 cc.
Glycerine	110 cc.
Syrup of raspberry	160 cc.
Distilled water, to make	1000 cc.

To utilize the preparation as an elixir of B vitamins, the following formula has been suggested:

Thiamin hydrochloride	0.125 Gm.
Riboflavin	0.042 Gm.
Pyridoxine hydrochloride	0.038 Gm.
Calcium pantothenate	0.038 Gm.
Nicotinic acid	0.375 Gm.
Elixir raspberry, to make	1,000.00 cc.

Each 8 cc. of this preparation contains 1 mg. of thiamin hydrochloride, 1/3 mg. riboflavin, 0.3 mg. pyridoxine hydrochloride, 0.3 mg. calcium pantothenate and 3 mg. of nicotinic acid. It has been observed that the elixir of raspberry is compatible with many other drugs, including salicylates, bromides, iodides, citrates, elixirs of three or five bromides, elixir of phenobarbital, elixir of iron, quinine and strychnine, and elixir of glycerophosphates.

Some glycerine-utilizing preparations are described in patents; most of them owned by pharmaceutical manufacturers. One such (4) describes how to make stable solutions of one or more of the B group vitamins by incorporation in an aliphatic polyhydric alcohol containing three carbon atoms. Glycerine, of course, is cited as being suitable for this purpose.

Although they are not so widely used as formerly, it is interesting to note that cod liver oil emulsions make frequent use of glycerine, which helps to carry the vitaminized oils in products that are more stable, more pleasing and more palatable. One modern combination which yields a permanent emulsion that may be diluted, is given by Bennett (5), as follows:

Cod liver oil	300.0 Gm.
Alcohol	60.0 cc.
Glycerine	50.0 Gm.
Water	500.0 cc.
Gum tragacanth	0.5 Gm.
Sodium bicarbonate	1.0 Gm.
Sodium benzoate	1.0 Gm.
Soybean lecithin	100.0 Gm.

Suspend the melted lecithin in the warm alcohol and glycerine mixture, and mix in the warm cod liver oil. Dissolve the gum tragacanth, benzoate and bicarbonate in the hot water, and add this solution to the first mixture. Agitate in a mechanical mixture for 10 to 20 minutes until a permanent creamy emulsion results.

Another modern cod liver oil emulsion, also containing other nutrients, uses pectin as the emulsifier (6). This consists of:

Cod liver oil	25.00 Gm.
Pure concentrated orange juice	15.00 Gm.
Citrus pectin ("Exchange" 100 grade)	3.25 Gm.
Glycerine	10.00 Gm.
Malt extract	20.00 Gm.
Distilled water	26.75 Gm.

Mix the glycerine and pectin to produce a smooth paste. Add the water and then the orange concentrate, stirring thoroughly during the addition. Add the malt extract and finally emulsify the oil into the mixture by adding it slowly in small amounts. Stir thoroughly. Prior to packaging, remove the entrapped air by vacuum deaeration or light centrifugal treatment and mix to insure uniformity.

Another modern variation has been listed recently by Holland (7). This cod liver oil emulsion calls for the use of:

Cod liver oil	50.0 cc.
Methyl cellulose	1.0 Gm.
Glycerine	1.0 cc.
Oil of bitter almond	0.2 cc.
Saccharin sodium	0.006 Gm.
Water, to make	100.0 cc.

Also noteworthy are vitaminic oil products in which glycerine is an important ingredient. According to the patent (8), a vitaminic oil such as a fish liver oil is used with glycerine, a mono-oleic acid ester of diglycerine, and sucrose—to form compositions which may be added to aqueous media, such as milk or water. These form stable emulsions or dispersions which may be subjected to refrigeration, long standing, boiling or centrifugation without separation.

During the last few years considerable interest has been focused on the development of stable, acceptable liquid preparations containing both water-soluble vitamins and vitaminic oils. As now frequently the case, products of this sort are protected by patents. Examination of the patent literature indicates that glycerine plays a prominent role in the formulation of such products.

According to one such patent (9), excellent, stable, completely water-dispersible multivitamin compositions can be prepared by incorporating the vitamins in a solvent consisting of ethyl alcohol and glycerine. In such preparations glycerine serves as a blending agent. In one example, 200 mg. of crystalline vitamin B, are mixed with 2.5 Gm. of crystalline vitamin C; then 12.5 Gm. of glycerine and 20 cc. of alcohol are added. When warmed slightly a clear solution is formed. To this solution is added 1.1 Gm. of a highly potent vitamin A concentrate and 0.1 Gm. of a vitamin D concentrate. Enough alcohol is added to bring the solution up to 100 cc. A brilliantly clear, homogeneous solution is formed which is readily dispersed in water without any separation of the oily concentrates.

Other examples are given, some using higher proportions of glycerine. Such preparations may be added to aqueous foods like milk, coffee, tea, chocolate or other flavored drinks, and to aqueous medicinal preparations, like tonics, to form stable products that are vitamin-fortified.

In a more recent case (10) methods are given whereby oils or fatty materials may be emulsified in glycerine to provide stable, non-aqueous emulsions. This is achieved by incorporating small amounts of alcohol-soluble proteins, called prolamines, into the glycerine. The resulting glycerine base, which is non-toxic and, except for its sweetening effect, substantially tasteless, has been found particularly suitable as a vehicle for vitamins. Not only are the fat-soluble types A, D, and E readily incorporated in the glycerine base, but also the water-soluble vitamins comprising the B complex group and vitamin C.

Not only is glycerine a useful adjunct in the preparation of orally administered vitamin preparations, but it is also used on occasion in topical preparations. Illustrative is the following vitamin

and proflavine ointment, as given (11) in the "Commonwealth Pharmaceutical Formulary" of Australia:

Vitaminized oil	120 minims
Proflavine sulfate	1/2 grain
Glycerine	10 minims
Yellow soft paraffin	1 oz.

Also interesting is the report by Gross (12) that the topical application of a vitamin B_1 solution is effective in treating herpes. The mixture consists of 1 cc. of thiamin hydrochloride solution containing 50 mg. of the vitamin in 3 cc. of glycerine. This medication is applied three times daily to the skin lesions. Gross states that he has employed this vitamin B_1-glycerine mixture for six months with excellent results. He has come to regard it as a specific for herpes and similar conditions.

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BOOK REVIEWS

A Survey of the British Pharmacopoeia 1948. 79 pages, including index; The Pharmaceutical Press, 17 Bloomsbury Square, London, W. C. Price 5s. 6d. (Postage 3d.)

This little volume comprises a series of lectures given by members of the British Pharmacopoeial Commission and other authorities. These lectures were for the purpose of acquainting pharmacists with the changes in pharmaceutical practice brought about by the new Pharmacopoeia which became official September 1, 1949. A total of six lectures are given with the original material somewhat amplified where needed. The titles and the lectures are as follows:

The British Pharmacopoeia 1948 by C. H. Hampshire;

Pharmaceutical Preparations by R. R. Bennett;

Parenteral Injections and Tablets by Prof. H. Berry;

Chemical Substances—Part I by A. D. Powell;

Chemical Substances—Part II by Prof. W. H. Linnell;

Crude Drugs by T. E. Wallis;

Biological Preparations by Sir Percival Hartley.

Although presented with respect to the changes in the British Pharmacopoeia, American pharmacists, pharmaceutical chemists and others interested in manufacturing and control will find this series of considerable interest. One is impressed with the speed at which British and American pharmacy are approaching one another, at least in their therapeutic armamentaria. This speaks well for the movement for an international pharmacopoeia, one of the few manifestations of future world peace and understanding.

L. F. TICE

A Text-Book of Inorganic Pharmaceutical Chemistry. By C. H. Rogers, T. O. Soine, and C. O. Wilson. Fourth Edition, 704 pages, 1948. Lea and Febiger, Philadelphia.

This work has been revised to conform to the United States Pharmacopeia XIII and National Formulary VIII. In addition, several important changes have been in the content of the book. Methods of quantitative analysis have been deleted, and industrial processes revised. Chemical properties, pharmacological actions, and therapeutic uses have been elaborated upon. Only those relatively simple organic compounds whose therapeutic activity resides principally in the inorganic portion of the molecule have been included. Certain non-official, inorganic compounds having therapeutic usefulness are also described.

Under each element is given information on the history, occurrence, physical and chemical properties, commercial manufacture and uses. Where feasible, there is also included tests for identity, laboratory preparation, pharmacological action, pharmaceutical preparations and uses of the element of its ions.

The salts of the element are then described, under much the same headings as for the elements.

First the official and then important non-official salts are included. In the chapter on Hydrogen, the ionization of acids, the Bronsted-Lowry concept of acids and bases, pH measurements and calculations are discussed. Throughout the book there are numerous chemical equations illustrating chemical properties and manufacturing processes.

This book is highly recommended as a valuable reference for students of pharmacy and for pharmacists.

L. A. Reber

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American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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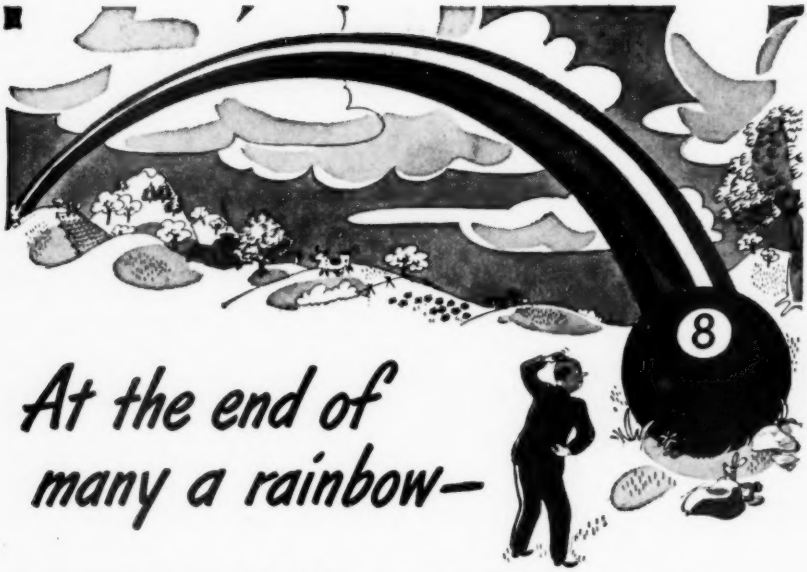

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